## REMARKS

Introductory Comments:

Claims 1-7, 10-21 and 41 were examined in the Office Action under reply and stand rejected under (1) 35 U.S.C. §102 (claims 1-3, 6, 7, 12, 13 and 41); and (2) 35 U.S.C. §103(a) (claims 1, 3-5, 10, 11, 14-21). These rejections are traversed for reasons discussed below.

Applicant notes with appreciation the rejoinder of claims 16-21 with the elected claims, as well as the withdrawal of all of the previous rejections.

Overview of the Above Amendments:

The specification has been amended at page 18 to correct an obvious typographical error.

Claims 1, 3, 16, 17 and 41 have been amended in order to recite the invention with greater particularity. Withdrawn claims 22-40 have been cancelled. Claims 4 and 5 have been canceled and the substance thereof incorporated into claims 1, 3 and 41. Claims 13 and 14 have also been cancelled and claims 16 and 17 have been amended to depend from claims 1 and 3, respectively, instead of from cancelled claims. The claims have additionally been amended to recite the expression or presence of the HCV immunogen for at least one month in the animal. Support for the above amendments can be found in the claims as filed, as well as throughout the specification at, e.g., page 7, first full paragraph.

The above amendments are made without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record.

Rejections Over the Art:

Claims 3, 7 and 13 were rejected under 35 U.S.C. §102(b) as anticipated by Gorczynski et al., *Cellular Immunol.* (1995) 160:224-231 ("Gorczynski"). Additionally, claims 1-3, 6, 7, 12, 13 and 41 were rejected under 35 U.S.C. §102(b) as anticipated by

Nakai et al., Blood (1998) 91:4600-4607 ("Nakai"). Applicant notes that claims 4 and 5 were not subject to the rejections over Gorczynski and Nakai. The substance of these claims has been incorporated into all of the pending independent claims. All remaining claims ultimately depend from these claims. Thus, these bases for rejection have been overcome and withdrawal thereof is respectfully requested.

Claims 1, 3-5, 10, 11 and 14-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Gorczynski in view of Nakai and further in view of Wakita et al., *J. Biol. Chem.* (1998) 273:9001-9006 ("Wakita"). Gorczynski is said to teach "the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal." Office Action, page 6. The Office correctly notes Gorczynski does not teach the immunogen is a protein encoded by a nucleic acid delivered by portal vein injection. Nakai is cited for teaching "that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal." Office Action, page 6. Wakiti is said to teach "conditional trangene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of transgenic mice results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection." Office Action, page 7. Applicant respectfully disagrees with the Examiner's assertion.

It is well settled that *prima facie* obviousness can only be established if the following three basic criteria are met: (1) there must be some suggestion or motivation to modify the reference; (2) there must be a reasonable expectation of success (for the modification and/or combination); and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991). The Office has not satisfied these criteria.

In particular, Gorczynski did not deliver DNA or an immunogenic protein to an animal. Rather, mice were rendered hyporesponsive to multiple minor incompatible skin allografts by pretreatment with irradiated lymphoid cells injected via the portal vein. The mice were administered the skin grafts 36 hours after injection and sacrificed 24, 48 and 120 hours post-grafting. See, page 226, last paragraph. In other experiments, mice were given spleen cells followed by skin grafts at 36 hours and sacrificed 10 days later. See, page 228, second column. Accordingly, nothing can be gleaned regarding the ability of an HCV immunogen to be expressed or present in an animal for at least one month.

Nakai and Wakita do not provide the missing link. Nakai relates to gene therapy, not nucleic acid immunization and is therefore not relevant to the presently claimed invention. Specifically, Nakai pertains to the delivery of the gene encoding human Factor IX, a therapeutic protein deficient in subjects with Hemophilia B. Delivery is to the liver because Factor IX is normally synthesized in the liver. See, e.g., page 4600, first column. Human Factor IX is not an immunogen as claimed in the present application and would not be expected to produce an immune response as it is an endogenous protein. Rather, if an immune response is present, it is normally directed against the vector used to deliver the therapeutic protein and renders expression short-lived due to the elimination of vector-transduced cells. See, e.g., page 4600, second column. Nothing in Nakai relates to the production of an animal model immunotolerant to a viral immunogen, let alone an HCV immunogen.

Wakita relates to the delivery of a vector encoding HCV core, E1, E2 and NS2 to fertilized mouse eggs. The mice produced did NOT express HCV proteins in the absence of Cre recombinase and therefore did not exhibit "sustained" expression of HCV genes as characterized by the Examiner. See, page 9005, second full paragraph. Rather, a recombinant adenovirus expressing Cre recombinase was delivered intravenously and mice were sacrificed 3 or 7 days after injection with the adenoviral vector and only then was HCV gene expression seen. These experiments have nothing whatsoever to do with providing an immunotolerant animal for screening for agents that modulate tolerance to an HCV

immunogen. There is no indication that sustained expression or presence of the HCV DNA was achieved as the animals were sacrificed at 3 or 7 days.

None of the cited art, either alone or in combination teaches or suggests methods and animals as claimed. As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified, does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Without a suggestion to modify the references evident in the prior art as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the foregoing, the rejection of the claims over the stated combination should be withdrawn.

Claims 1, 3, 10, 11, 16, 17, 20 and 21 were rejected under 35 U.S.C. §103(a) as being unpatentable over Gorczynski in view of Nakai, further in view of Wakita, and further in view of PCT Publication WO 97/47358 to Donnelly et al. ("Donnelly"). Gorczynski, Nakai and Wakita are applied as described above. Donnelly is said to teach a nucleic acid encoding the HCV NS5a gene which can be used to raise an immunological response to HCV. However, as with Gorczynski, Nakai and Wakita, Donnelly does not pertain to methods of achieving sustained expression or production of an HCV immunogen in order to provide an immunotolerant animal, by delivery to the liver. Rather, Donnelly pertains to delivery of vaccines with optimized HCV DNA sequences into muscle in order to prevent HCV infection in humans, NOT to provide an immunotolerant non-human animal with which to study HCV infection. See, e.g., page 1, lines 16-21; page 3, lines 1-8; page 10, line 32 through page 11, line 2; page 11, lines 29-33. In fact, there is no expression data in the application whatsoever, let alone evidence of sustained expression of an HCV immunogen.

Rather, all of the examples in Donnelly merely describe production of optimized genes and expression constructs containing the genes.

Accordingly, as with the combination above, this combination also fails to teach or suggest the claimed invention. Thus, this basis for rejection should also be withdrawn.

## CONCLUSION

Applicant respectfully submits that the claims define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please send all further written communications in this case to:

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